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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,243	12/27/2001	Karen L. Fearon	377882001800	8533

25226 7590 08/01/2005

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EXAMINER	
DUFFY, PATRICIA ANN	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 08/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/033,243	FEARON ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *5-8 and 27-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,9-26,47 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2002, 2003X2*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The response to the restriction requirement filed 3-2-05 has been entered into the record.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code at page 46. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Information Disclosure Statement

The information disclosure statements filed 7-21-03, 4-28-03 and 4-22-02 have been considered. Initialed copies are enclosed.

Election/Restrictions

Applicant's election with traverse of Group comprising SEQ ID NO:132 in the response of 3-2-05 is acknowledged. The traversal is on the ground(s) that each nucleic acid is not a separate group because of the recited common generic structure of claim 1 and does not represent a search burden. This is not found persuasive because the alternatives recited in claim 1 do not provide for a common core structure that could be searched for all the claimed nucleic acids. Alternatives at the positions do not provide for a core structure that is identical or common to all the independently claimed nucleic acids of SEQ ID NOS:1, 2, 18, 19,67-80 and 132. As such, the independently claimed sequences

do not have a common core structure to all and as such would place an undue search and examination burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claims 5-8 and 27-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the response filed 3-2-05.

Claim Objections

Claims 9-25, 47 and 48 are objected to because of the following informalities: The claims are alternatively drawn to non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-4, 9-19, 22-26 and 47are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claimed invention is drawn to a product of nature. Products of nature are not patentable because they do not reflect the "hand of man" in the production of the product or manufacturing process.

The claimed invention is drawn to a product of nature. Products of nature are not patentable because they do not reflect the "hand of man" in the production of the product

or manufacturing process. *Diamond v. Chakrabarty*, 206 USPQ 193 (1980). Additionally, purity of naturally occurring product does not necessarily impart patentability. *Ex parte Siddiqui* 156 USPQ 426 (1966). However when purity results in new utility, patentability is considered. *Merck Co. V. Chase Chemical Co.* 273 F. Supp 68 (1967). See also American *Wood v. Fiber Disintergrating Co.*, 90 US 566 (1974); *American Fruit Growers v. Brogdex Co.* 283 US 1 (1931); *Funk Brothers Seed Co. V. Kalo Innoculant Co.* 33 US 127 (1948). Filing of arguments and evidence of a new utility imparted by the increased purity of the claimed invention *and amendment to the claims to recite the essential purity* of the claimed products is suggested to obviate this rejection. For example, "An isolated sequence...".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 9-26, 47 and 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey

to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to "immunomodulatory polynucleotides". The term "immunomodulatory" includes down-regulation or suppression of the immune response. Applicants have specifically defined "immunomodulatory polynucleotide to include immunostimulatory as well as immunosuppressive effects" (page 12. lines 11-25). Down-regulation or suppression of an immune response by tolerizing mechanisms. Immunological tolerance is defined as the induction of specific non-reactivity to an antigen capable in other circumstances of inducing active cell-mediated or humoral immunity. Tolerance may be due to anergy, clonal deletion or active suppression of antigen-specific clones of T or B lymphocytes (page 93, Herbert et al, The Dictionary of Immunology, Academic Press, 1995). The specification is devoid of description of any polynucleotide that performs down regulation of the immune response by known mechanisms of the art. While the specification teaches immunostimulatory nucleic acids, it does not teach immunosuppressive nucleic acids. As such, one skilled in the art would recognize that Applicants were not in possession of the claimed invention as it relates to "modulation" of the immune response as claimed.

Claims 1-4, 9-26 and 47-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated immunostimulatory oligodeoxynucleic acids consisting of SEQ ID NOs:18, 38 and 59, wherein the immunostimulatory polynucleotide is fully modified phosphorothioate oligodeoxynucleotides and said immunostimulatory oligodeoxynucleic acids increase IFN-gamma or IFN-alpha and compositions comprising such and wherein the immunostimulatory nucleic acid is optionally complexed with cationic poly(lactic acid, glycolic acid) microspheres, it does not reasonably provide enablement for immunomodulatory nucleic acids, immunostimulatory nucleic acids in general, and biodegradable microcarriers in general, or oligoriboxynucleotides,

immunostimulatory sequences liked to cationic poly(lactic acid, glycolic acid) by any means or biodegradable carriers in general. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to "immunomodulatory polynucleotides". The term "immunomodulatory" includes down-regulation or suppression of the immune response. An immune response is art defined as "The specific response to antigen. Thus, includes the responses of cell-mediated immunity, humoral immunity and, in its widest sense immunological tolerance" (page 88, Herbert et al, The Dictionary of Immunology, Academic Press, 1995). Applicants have specifically defined "immunomodulatory polynucleotide to include immunostimulatory as well as immunosuppressive effects" (page 12. lines 11-25). Down-regulation or suppression of an immune response occurs by tolerizing mechanisms. Immunological tolerance is defined as the induction of specific non-reactivity to an antigen capable in other circumstances of inducing active cell-mediated or humoral immunity. Tolerance may be due to anergy, clonal deletion or active suppression of antigen-specific clones of T or B lymphocytes (page 93, Herbert et al, The Dictionary of Immunology, Academic Press, 1995). The term is also defined to include an immune response that is shifted towards a Th1-type response that is typically considered cellular immune response whereas Th2-type are generally considered humoral or antibody-based.

The teachings of the specification are limited to a demonstration that fully modified phosphorothioate oligodeoxynucleotides of SEQ ID NOS: 18, 38 and 59 provide for immunostimulation by means of increased antigen-specific IgG when administered to mice in conjunction with the antigen. Strictly speaking the response of other disclosed SEQ ID NOS that produce increased levels of INF-gamma and INF-alpha from mixed cell cultures is not necessarily indicative of an immune response. The source of the INF-gamma and INF-alpha produced in response to the ISS sequence is not taught by the specification as filed. It is noted that the only *in vivo* immunostimulatory response studied

was the ability to generate antigen-specific IgG antibody. The generation of antibody is admitted by applicants at page 12, to be largely a Th2-like response. Therefore, the data presented in Examples at pages 85-103 of the specification does not demonstrate for the skilled artisan that the response generated was Th1 mediated. No cytotoxic cellular responses were measured nor was any delayed type-hypersensitivity response measured. No delineation of the subtype of IgG antibody produced was studied and therefore, the skilled artisan cannot conclude that the response was Th1-like or mediated. Further, there is not one assay that indicates that the claimed nucleic acids possess the ability to downregulate any immune response by means of active suppression, tolerance or anergy as contemplated falling within the scope of "immunomodulatory". The art of record establishes that the biological response to the administration of CpG containing oligonucleotides vary, depending upon the mode of administration and the organism (McCluskie et al , Molecular Med, 5(5):287-300, 1999, especially page 296 and Krieg et al, Immunology Today 21(10):521-526, 2000, especially page 524). CpG-ODNs have multiple stimulatory effects on different cells, such as lymphocytes, dendritic cells, macrophages, natural killer (NK) cells and T cells (see page 619 Wohlleben et al, TRENDS in Immunology 22(11):618-626, 2001). As such, the ability of any claimed ISS-containing CpG oligonucleotide to be "immunostimulatory" to immunomodulate a or generate a Th1-like immune response alone or versus a Th2-like immune response has not been demonstrated by this specification as filed. The source of the IFN-gamma has not been ascertained to be related to specific immune cells (i.e. the source of the IFN-gamma not identified as T-cell derived). Isolated T cells were not evaluated and T-cell depleted populations were not evaluated for IFN-gamma production. Any Th1-like response to antigen was not evaluated either *in vitro* or *in vivo*. The Th2-like cytokines were not evaluated, the IgG subclass of antibody not evaluated and therefore the skilled artisan can not make a reasonable conclusion regarding the generation of a Th1-type response as opposed to a Th2-type response. Therefore, "immune stimulation" was not measured in all but SEQ ID NOS:18,

38 and 59. Further, a switch in T helper response (i.e. immunomodulate as described at page 12 of the specification) can only be ascertained in a live animal model such as that described by Wohlleben et al *supra* and this specification is devoid of data using known animal models reflective or typical of a Th2-response such that an effective modulation to a Th1 has been demonstrated. Further, Kline et al (Am J. Physiol. Lung Cell Mol. Physiol., 283:L170-L179, 2002; Kline et al J. Immunol, 160:2555-2559, 1998) teaches that a single treatment of CpG-ODN alone was ineffective in reducing the manifestations consistent with asthma in an animal model (page L172, page 178, paragraph bridging columns 1-2). As such, the ability of CpG's inducing cytokines does not correlate with its ability *in vivo* to demonstrate immunomodulation. Further, Kline et al 2002, teaches that splenocytes from OVA-treated mice did not develop antigen-specific Th1 phenotype. As such, the specificaiton as filed is devoid of data that indicates that the broadly claimed ISS nucleic acids possess immunomodulatory activity or immunostimulating activity as claimed.

With respect to linkage modifications, combinations thereof or ribose nucleotides or combinations with deoxynucleotides and complexed or linked to biodegradable carriers, Weiner (J. Leukocyte Biology, 68:456-463, 2000) states that the molecular mechanisms of CpG oligonucletoides' immunostimulatory effects are not yet understood (see page 461). While the biological effects of some chemical modifications have been studied for CpG containing oligonucletoides, the incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable (see Agarwal et al, Molecular Med, Today, 6:72-81, 2000, especially pp 78-80). Further, the art of record teach that the phosphorothioate analogs are the most potent in immune stimulation (see Zhao et al (Biochemical Pharmacology, 51:173-182, 1996, page 173 (abstract); of record in PTOL-1449) and there is no evidence of record that any sequence that is not fully phosphorothiolated provides for immune stimulation in any model. Zhao et al teaches that modifications unpredictably effect the ability of modified CpG containing oligodeoxynucleotides to provide for immune stimulation as measured by *in vitro* and *in*

vivo. Additionally, the length of the oligonucleotide impacts its ability to induce interferon gamma production in mixed splenocyte cultures. Yamamoto et al (Antisense Research and Development 4:119-122, 1994) teach that immunostimulatory activity of oligonucletoides of 18 bases or more in length was observed and was proportional to the base length, with a maximum at 22-30 bases and oligonucleotides 16 bases or less in length were not active even if they possessed the palindromic sequence (see abstract). This specification fails to teach that oligonucletoides having the minimal palindromic sequence of 10 residues as set forth in SEQ ID NO:62 are effective immunomodulators, immunosuppressors or immunostimulators as instantly claimed. With respect to coupling to microspheres of different compositions, it is noted that cross-linked immobilized CpG-ODN do not provide for effective immune stimulation (Manzel et al, Antisense and Nucleic Acid Drug Development 9:459-464, 1999; of record in PTOL-1449). As such, in the absence of the demonstration of activity of a number of different ISS complexes (covalent and non-covalent) on different carriers, the claims are not broadly enabled for linked by any means such as covalent conjugation in any biodegradable carrier.

The amount of direction or guidance presented in the specification and the presence or absence of working examples is a hindrance to using the claimed invention in the manner contemplated by the specification for the scope of the claimed invention. Applicants have not provided guidance as to the generation of a Th1-response. In view of the pleotropic effects of CpG's in inducing IFN-gamma in numerous cell types and the lack of description or data demonstrating either a switch in a antigen-specific Th2 to Th1 response *in vivo* or the generation of an antigen-specific Th1 response *in vitro* or *in vivo*, the specification is not broadly enabled for the now claimed invention. In view of the foregoing art, one skilled in the art would not accept on its face the limited example of 3 ISS oligodeoxynucleotides given in the specification as being correlative or representative of immunomodulation (suppression or switch from Th2 to Th1) or generation of a Th1-type response *per se* or representative of the activity of the claimed decameric sequence.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments

Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-3, 7, 9, 11, 15, 16, 17, 18, 19 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Jefferson et al (US Patent No. 5,879,906, issued March 9, 1999).

Jeffereson et al teach fragments of the gus operon of *E. coli*. The fragments are pMEL6 and pMEL7 as presented in the 48-mer and 18-mer in Figure 18. The sequences comprise the sequence ..TCGAACGAACGTTCG.... As such, the sequence of the prior art meets the claimed invention. The biological activity is inherent to the structure.

Since the Office does not have the facilities for examining and comparing Applicant's nucleic acid with the nucleic acid of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the nucleic acid of the prior art does not possess the same functional characteristics of the claimed nucleic acid). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 619 F.2d 67, 205 USPQ 594 (CCPA 1980).

Claims 1-3, 15-19, 22, 23, 26, 48 and 49 are rejected under 35 U.S.C. 102(e) as being anticipated by Doucette-Stamm et al (US Patent No. 6800744, issued October 5, 2004 with priority to provisional document 60/051,533 filed July 2, 1997).

Doucette-Stamm et al teach a nucleic acid sequence set forth in SEQ ID NO:1794 that encodes a polypeptide of the invention. SEQ ID NO:1794 is from the bacterium *Streptococcus pneumoniae*. The nucleotide residues 37-46 of SEQ ID NO: 1794 is 100% identical to SEQ ID NO:77. The nucleic acid of Doucette-Stamm et al is 480 nucleotides long. As such, the structural sequence of the prior art meets the claimed invention. The biological activity is inherent to the structure. Doucette-Stamm et al teach the term

nucleic acid encompasses RNA, DNA, double stranded as well as coding and antisense single strands (column 6, lines 39-44). Doucette-Stamm et al teach the nucleic acids of the invention in vaccine formulations (column 38, lines 27-34) and compositions comprising the nucleic acids and pharmaceutically acceptable carriers (column 39, lines 30-35) and delivery methods including biodegradable microcapsules, ISCOMS, liposomes, viral vectors virus-like particles (see column 39, line 48-column 40 line 35). Doucette-Stamm et al teach nucleic acid probes comprising at least 8, 12, 20 consecutive nucleotides of the invention for use as hybridization probes (see column 6, lines 51-61 and column 7, lines 20-35). Doucette-Stamm et al teach kits containing nucleic acids of the invention for diagnostics or hybridization and instructions for use (see column 42, line 53 to column 43, line 7).

Status of the Claims

All claims stand rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-Th 6:30 am - 6:00 pm. If attempts to

reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patricia A. Duffy, Ph.D.
Primary Examiner
Art Unit 1645